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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of McBride and Griffiths
U.S. Serial No.: 09/676,783
Filed: October 2, 2000
Attorney Docket No.: 018733/0997
For: RADIOMETAL-BINDING PEPTIDE ANALOGUES

BRIEF ON APPEAL

Appeal from Group 1639

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Appellants hereby appeal the January 13, 2003 rejection of the above-identified application to the Board of Patent Appeals and Interferences.

I. REAL PARTY IN INTEREST

Immunomedics, Inc., Morris Plains, NJ, owns the entire right, title and interest in the present patent application, as evidenced by an assignment recorded on 01/20/1998, at Reel 8927, Frame 0059. Immunomedics is, therefore, the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other appeals or interferences pertaining to the instant invention.

III. STATUS OF CLAIMS

Claims 24 - 43 are pending. All claims ultimately depend from claim 24. A copy of the claims, as amended thus far, is presented in APPENDIX I.

IV. STATUS OF AMENDMENTS

An amendment after final was filed on April 14, 2003. In the subsequent Advisory Action mailed on May 1, 2003, the Examiner indicated that the amendment would be entered for purposes of an appeal.

V. SUMMARY OF THE INVENTION

The invention relates to derivatives of biologically useful cyclic and acyclic peptides in which one or more amino acid side chains or a segment attached to the peptide chain contain chelating moieties that can tightly bind metal ions, including radionuclides. The labeled peptides carry the metal to specific *in vivo* targets such as receptors and antigens, and are useful for radiodiagnostic imaging, therapy and radiotherapy. The peptides can bind radionuclides while retaining the ability to specifically bind to the peptide receptor. The

radiolabeled peptides can then be used to image or treat a tumor, an infectious lesion, a myocardial infarction, a clot, an atherosclerotic plaque, or a normal organ or tissue.[1]

Radiolabeled peptides such as those claimed in this application are useful in the diagnosis and therapy of a variety of human disease states that are characterized by overexpression of peptide hormone receptors. Thus, for example, it has been shown that radiolabeled analogues of LHRH (luteinizing hormone releasing hormone) and somatostatin selectively bind to hormone-sensitive tumors characterized by cell-surface overexpression of LHRH hormone receptors. Similarly, peptide hormone analogues such as ^{123}I-vasoactive intestinal peptide (VIP), ^{99m}Tc-P829, ^{111}In-DTPA Octreotide and ^{111}In-bisMSH-DTPA have been used to image human tumors that over express VIP, somatostatin, and melanocyte stimulating hormone (MSH) receptors. *See* Virgolini *et al.*, *Engl. J. Med. 169*:1116 (1994); Virgolini *et al.*, *J. Nucl. Med. 36*:1732, (1995); Pearson *et al.*, *J. Med. Chem. 39*:1361, (1996); Krenning *et al.*, *J. Nucl. Med. 33*:652 (1992); and Wraight *et al.*, *Brit. J. Radiol. 65*:112 (1992).[2]

VI. ISSUE ON APPEAL

The sole issue on appeal is whether claims 24 - 40, 42 and 43 comply with 35 U.S.C. § 112, first paragraph.

Claims 24 - 40, 42 and 43 stand rejected in a January 13, 2003 Office Action on the grounds that the aforementioned claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO alleges that at the time appellant's application was filed, the extent to which the claimed radiolabeled cyclic peptides have been used is only in the diagnosis of specific tumors. The PTO has taken the position that treatment of even a specific tumor with the claimed radiolabeled cyclic peptides, if anything, simply looks promising.

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[1] See page 1, lines 6 – 14 of the Specification.
[2] See page 1, lines 15 – 34 of the Specification.

VII. GROUPING OF THE CLAIMS

The claims all stand or fall together.

VIII. SUMMARY OF THE ARGUMENT

The PTO erred when it held that claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors, at the time the application was filed, had possession of the claimed invention.

Contrary to the PTO's position, Appellants were in possession of the claimed invention: a method of treating a tumor using the claimed radiolabeled peptides. First, the Specification describes radiolabeling and *in vitro* experiments. Second, at the time the application was filed, the level of skill in the art to which the invention pertains was such that it is not necessary for Appellants to include much more detail in the Specification, in addition to the radiolabeling and *in vitro* experiments described therein, to demonstrate that they were in possession of a method for treating a tumor using the claimed radiolabeled peptides. Indeed, at the time the application was filed, it was known that many peptides closely related to those claimed in claim 24 could be used in radionuclide therapy to treat tumors. The Specification, therefore, is enabling for the treatment of tumors with the claimed radiolabeled peptides. Thus, claim 24, and the claims which depend upon it, should not have been rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement.

IX. ARGUMENT

In the Office Action dated July 31, 2002, the PTO asserts that the claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors, at the time the application was filed, had possession of the claimed invention.

In the response to the July 31, 2002 Office Action,[3] Appellants rebutted the PTO's assertions by relying on MPEP Section 2163 which provides, in relevant part, that the analysis of whether the Specification complies with the written description requirement calls for the PTO to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. The guidelines in Section 2163 themselves provide that "***[g]enerally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement.***" Information which is well known in the art need not be described in detail in the Specification. *See*, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

In support of Appellants' position, Appellants submitted journal articles that illustrated the level of skill in the art to which the invention pertains. These articles demonstrated that, at the time the application was filed, it was known that peptides related to those claimed in the present application where promising *in vitro* candidates for the treatment of certain tumors. Further, these articles demonstrated that the *in vitro* results could be extrapolated to the use of such peptides in radionuclide therapy to treat certain tumors *in vivo*.[4] In the response to the January 13, 2003 Office Action, Appellants submitted additional articles that demonstrated that

[3] See page 6 of the Response filed October 31, 2002.

[4] The U.S. Court of Appeals for the Federal Circuit, in *Rey-Bellet* and *Kawai*, has implied that "a particular pharmacological activity identified with prior art compounds may have probative value as to the fact that the compound of the [invention] possesses this particular pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the [invention]." *Cross v. Iizuka* 753 F.2d 1040, 1048 (Fed. Cir. 1985) citing *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1385 (CCPA 1974); *Kawai v. Metlestics*, 480 F.2d 880, 890 (CCPA 1973). Although Appellants have provided journal articles which describe how peptides related to those claimed in the present application have been used for the treatment of certain tumors *in vivo*, Appellants offer that it is well settled that *in vitro* data is sufficient, in many cases, to satisfy the utility and the enablement requirement of 35 U.S.C. § 112, first paragraph. *See Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985) ("*in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* results, i.e., there is a reasonable correlation therebetween.").

the extrapolation of *in vitro* results to *in vivo* radio therapeutic efficacy was indeed appropriate. These articles demonstrated that peptides related to those claimed in the present application can and have been used in radionuclide therapy to treat tumors in rat animal models and in human patients.

The journal articles which demonstrated *in vitro* and *in vivo* results using peptides related to those claimed in the present application are summarized below.

In vitro

de Jong *et al.*, *Cancer Research 58*: 437-441 (1998) (EXHIBIT A)

de Jong *et al.* demonstrated that ^{111}In-labeled somatostatin analogs showed high and specific binding *in vitro* to somatostatin receptors in mouse pituitary AtT20 tumor cell membranes. de Jong *et al.* also showed that all of the compounds that were evaluated, namely, [DTPA^0]octreotide, [DTPA^0,Tyr^3]octreotide, [DTPA^0,D-Tyr^1]octreotide, [DTPA^0,Tyr^3]octreotate, and [DOTA^0,Tyr^3]octreotide, showed specific internalization in rat pancreatic tumor cells. In addition, de Jong *et al.* showed that these results translated to *in vivo* models. For example, biodistribution studies showed that radioactivity in the octreotide-binding, receptor expressing tissues and tumor-to-blood ratios were significantly higher when [^{111}In-DTPA^0,Tyr^3]octreotide, [^{111}In-DTPA^0,Tyr^3]octreotate, and [^{111}In-DOTA^0,Tyr^3]octreotide were used than when [^{111}In-DTPA^0]octreotide was used. Finally, de Jong *et al.* characterize radiolabeled [DTPA^0,Tyr^3]octreotide, and especially [DTPA^0,Tyr^3]octreotate and their DOTA-coupled counterparts as "most promising for scintigraphy and radionuclide therapy of [somatostatin] receptor-positive tumors in humans.

Lewis *et al.*, *J. Med. Chem. 42*: 1341-1347 (1999) (EXHIBIT B)

In a study which illustrated the structure activity relationship of various somatostatin analogs related to those described by de Jong *et al.* (*supra*), Lewis *et al.* compared the *in vitro*

binding, *in vitro* tumor cell uptake, and *in vivo* distribution of [^{64}Cu-TETA,Tyr^3]octreotide and [^{64}Cu-TETA]octreotate with that of [^{64}Cu-TETA,Tyr^3]octreotate and [^{64}Cu-TETA]octreotide. Appellants note that they have used the same type of nomenclature used in the de Jong *et al.* to describe the peptides of Lewis *et al.* Lewis *et al.* demonstrated that, while all of these peptides displayed affinity for somatostatin receptors on CA20948 rat pancreatic tumor membranes, [^{64}Cu-TETA]octreotate and [^{64}Cu-TETA,Tyr^3]octreotate showed the highest affinity for the receptors. Biodistributions in CA20948 tumor-bearing rats showed receptor mediated uptake of the ^{64}Cu-labeled peptides in somatostatin-rich tissues, including the pituitary adrenals, pancreas, and tumor. Lewis *et al.* found that [^{64}Cu-TETA,Tyr^3]octreotate exhibited the highest tumor uptake of all of the peptides studied.

Lewis *et al. Clinical Cancer Research 5*: 3608-3616 (1999) (EXHIBIT C)

In this study, Lewis *et al.* mention a previous study which showed that [^{64}Cu-TETA]octreotide significantly exhibited the growth of somatostatin receptor-positive CA20948 rat pancreatic tumors in Lewis rats. Anderson *et al.*, *J. Nucl. Med. 39*: 1944-1951 (1998). In the current study, Lewis *et al.* found that a single dose of 15 mCi of [^{64}Cu-TETA,Tyr^3]octreotate was shown to be more effective in reducing tumor burden than the same dose of [^{64}Cu-TETA]octreotide. Lewis *et al.* also found that in multiple dose experiments, complete regression of tumors was observed for all rats treated with 3 x 20 mCi of [^{64}Cu-TETA,Tyr^3]octreotate; with no palpable tumors for approximately 10 days. Lewis *et al.* found that the mean survival time of the rats was nearly twice that of controls.

In vivo

Rat Animal Model

Bugaj *et al. Nucl. Med. Biol. 28*: 327-334 (2001) (EXHIBIT D)

Using animal tumor models, Bugaj *et al.* evaluated the radiotherapeutic efficacy of the radiolabeled somatostatin analog CMDTPA-Tyr^3-octreotate: a compound related to the

radiolabeled peptides claimed in the present invention. Bugaj *et al.* focused on the beta-emitting nuclide, ^{153}Sm, chelated to the somatostatin analog, CMDTPA-Tyr^3-octreotate. Bugaj *et al.* found that suppression of tumor growth rate was observed in all animals treated with ^{153}Sm-CMDTPA-Tyr^3-octreotate compared to untreated controls. Greater inhibition of tumor growth was observed in animals that received multiple doses.

On page 332, column 2, of the Bugaj *et al.* article, it is mentioned that "[a]dditional studies are necessary to determine whether the high pancreatic uptake observed in rats will also be found in humans." Bugaj goes on to say that "[r]esults with other octreotate derivatives in primates, where no apparent pancreas uptake is observed in scintigraphs, suggest that this will not be the case." Appellants note, and the skilled artisan will recognize, that tumors in locations other than the pancreas may be treated using the compound reported by Bugaj *et al*, notwithstanding Bugaj *et al.*'s comments vis-à-vis testing of the reported compounds in primates.

Human Studies: Beyond the Rat Animal Model

Paganelli *et al.*, *Cancer Biother. Radiopharm. 14*: 477 – 483 (1999) (EXHIBIT E)

When the instant application was filed, Paganelli *et al.* had already demonstrated that a compound related to the radiolabeled peptides claimed in the present invention, can be used to treat tumors in humans. Paganelli *et al.* reports the dosage, safety profile and therapeutic efficacy of ^{90}Y-labeled DOTA-[D-Phe^1-Tyr^3]-octreotide (DOTATOC) when patients with cancers expressing somatostatin receptors are treated with this compound. Paganelli *et al.* also showed that out of 5 patients that were treated, complete and partial tumor mass reduction was measured in 25% of patients, along with 55% showing stable disease and 20% showing progressive disease.

In a 2001 journal article, Paganelli *et al.* reported the results from treatment of 30 patients with DOTATOC. Paganelli *et al.*, *Eur. J. Nucl. Med. 28*: 426 – 434 (2001). Paganelli *et al.* demonstrated that complete or partial tumor mass reduction occurred in 23% of

patients; 64% had stable and 13% progressive disease. Both of the reports by Paganelli *et al.* are congruent with the notion that compounds such as those claimed in the present invention can be used to treat tumors in humans.

Kwekkeboom *et al.*, *Eur. J. Nucl. Med. 28*: 1319-1325 (2001) (EXHIBIT F)

Kwekkeboom *et al.* recognized and demonstrated that ^{177}Lu- and ^{111}In-labeled somatostatin analogs were effective in treating tumors in animal models. For example, when the somatostatin analog [DOTA^0,Tyr^3]octreotate, a compound related to the compound used by Paganelli *et al.*(*supra*) and to the compounds claimed in the present invention, was labeled with the beta- and gamma-emitting radionuclide ^{177}Lu, it had a favorable impact on tumor regression and animal survival in a rat model. Because of these advantages Kwekkeboom decided to compare [^{177}Lu-DOTA^0,Tyr^3]octreotate with [^{111}In-DTPA^0]octreotide in six *human* patients with somatostatin receptor-positive tumors. From their comparative experiments, Kwekkeboom *et al.* concluded that [^{177}Lu-DOTA^0,Tyr^3]octreotate demonstrated higher absorbed doses in most tumors, with about equal doses to potentially dose-limiting organs.

In addition to their own findings, Kwekkeboom *et al.* report a study by Otte *et al.* that showed that five human patients suffering from neuroendocrine tumors were treated successfully with [^{90}Y-DOTA^0-Tyr^3]octreotide. The Kwekkeboom *et al.* article also cites results of a study by Valkema *et al.* using [^{90}Y-DOTA^0-Tyr^3]octreotide treatment in a multicenter trial in 22 end-stage patients with progressive disease. Valkema *et al.*, *J. Nucl. Med. 41*: 111P (2000). Valkema *et al.* demonstrated that when these patients were treated with [^{90}Y-DOTA^0-Tyr^3]octreotide, a partial tumor response was observed in two patients, a minor response was observed in three patients and a stable disease was observed in ten patients.

The journal articles summarized above show the level of skill in the art at the time the application was filed. Further, the Specification, at page 44, line 4, to page 49, line 5, (i.e., Examples 10 - 12) teaches the skilled artisan (a) how to attach the radiolabel (^{99m}Tc and ^{188}Re)

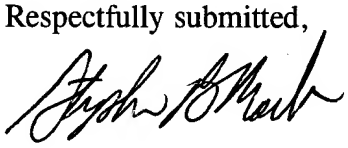
to the inventive peptides and (b) protocols for, and results from *in vitro* assays using human breast adeoncarcinoma cell lines MCF-7, SK-BR-3, and MDA-MB 231 and the inventive peptides. As discussed above, the case-law and the references submitted as Exhibits A – E both establish that extrapolation from *in vitro* data to *in vivo* utility is appropriate. Therefore, based on the disclosure of the Specification and the skill in the art demonstrated in the numerous articles summarized above, Appellants submit that the ordinary skilled artisan would know how to use radiolabeled peptides, such as those disclosed and claimed in the present application, to treat tumors. Therefore, pursuant to MPEP section 2163, it is not necessary for Appellants to describe in the Specification how the claimed radiolabeled peptides would be used to treat tumors, beyond what is already described in the Specification.

X. CONCLUSION

The PTO erred when it held that the claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors, at the time the application was filed, had possession of the claimed invention. Appellants have pointed to sections in the Specification where radiolabeling results and *in vitro* assays are described. Appellants have also shown that the level of skill in the art was such that it was not necessary to describe in the Specification how the radiolabeled peptides claimed in this application would be used to treat tumors. Appellants have demonstrated this by submitting various journal articles that show that the ordinary skilled artisan would know how to use radiolabeled peptides such as those disclosed and claimed in the present application to treat tumors. Accordingly, the instant Specification not only complies with the written description requirement, but it also demonstrates that Appellants had possession of the claimed invention.

Accordingly, Appellants respectfully urge the Honorable Board of Patent Appeals and Interferences to reverse the rejection of claims 24 – 40, 42 and 43 under 35 U.S.C. § 112, first paragraph and pass this application on to allowance.

Respectfully submitted,



Stephen B. Maebius
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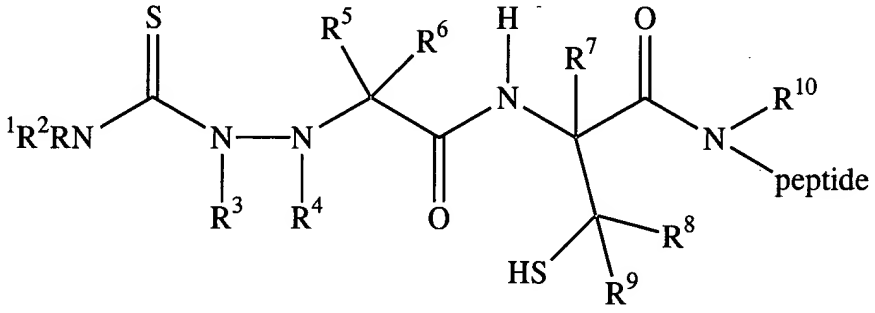
XI. APPENDIX I

24. A method of treating a tumor, comprising administering to a human patient a radiolabeled peptide and a pharmaceutically acceptable carrier, wherein said peptide comprises a radiometal-binding moiety comprising the structure:



wherein R^1, R^2, and R^3 independently are selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_6 cycloalkyl, substituted C_3-C_6 cycloalkyl, heterocycloalkyl, C_6-C_{12} aryl, C_6-C_{12} substituted aryl, heteroaryl, substituted heteroaryl, alkaryl, and a protecting group, provided that at least one of R^1, R^2, or R^3 is H,

R^5, R^7, R^8, R^9 and R^{10} independently are selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_6-C_{12} aryl, and substituted C_6-C_{12} aryl, and R^8 and R^9 together or R^7 and R^9 together may form a cycloalkyl or substituted cycloalkyl ring,

R^4 and R^6 together form a direct bond or are independently selected from the group consisting of C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_6-C_{12} aryl, and substituted C_6-C_{12} aryl, and wherein NR^{10} is located at the N-terminus of said peptide, or is located on an amino acid side chain of said peptide.

25. A method according to claim 24, wherein R^1 is H.

26. A method according to claim 24, wherein R^3 is H.

27. A method according to claim 24, wherein R^4 is H.

28. A method according to claim 24, wherein R^4 and R^6 together form a direct bond.

29. A method according to claim 24, wherein R^5 is H.

30. A method according to claim 24, wherein NR^{10} is located at the N-terminus of said peptide.

31. A method according to claim 24, wherein NR^{10} is located on an amino acid side chain of said peptide.

32. A method according to claim 25, wherein R^2 is lower alkyl or substituted or unsubstituted phenyl.

33. A method according to claim 32, wherein R^2 is H.

34. A method according to claim 33, wherein R^3 is H.

35. A method according to claim 34, wherein R^4 and R^6 together form a direct bond.

36. A method according to claim 34, wherein R^5 is H.

37. A method according to claim 36, wherein R^7 , R^8, and R^9 each are H.

38. A method according to claim 37, wherein R^2 is phenyl.

39. A method according to claim 37, wherein R^2 is methyl.

40. A method according to claim 24, wherein R^8 and R^9 are methyl.

41. A method according to claim 24, wherein said peptide is selected from the group consisting of:

(Chel)γAbuNle<u>DHF$_d$ RWK</u>-NH_2, (SEQ ID NO:1)

(Chel)γAbuHSDAVFTDNYTRLRKQMAVKKYLNSILN-NH_2, (SEQ ID NO:2)

KPRRPYTDNYTRLRK(Chel)QMAVKKYLNSILN-NH_2, (SEQ ID NO:3)

(Chel)γAbuVFTDNYTRLRKQMAVKKYLNSILN-NH_2,

(Chel)γAbuYTRLRKQMAVKKYLNSILN-NH_2, (SEQ ID NO:4)

HSDAVFTDNYTRLRK(Chel)QMAVKKYLNSILN-NH_2, (SEQ ID NO:5)

(SEQ ID NO:6) <GHWSYK(Chel)LRPG-NH_2, <GHYSLK(Chel)WKPG-NH_2, (SEQ ID NO:7)

$AcNal_d$ Cpa_d W_d SRK_d (Chel)$LRPA_d$ -NH_2, (SEQ ID NO:8)

(SEQ ID NO:9) (Chel)γAbuSYSNleDHF$_d$ RWK-NH_2, Ac-HSDAVFTENYTKLRK(Chel)QNleAAKKYLNDLKKGGT-NH_2, (SEQ ID NO:10)

(SEQ ID NO:12) Nal$_d$ Cpa$_d$ W$_d$ SRK$_d$ (Chel)WKPG-NH_2, <GHWSYK$_d$ (Chel)LRPG-NH_2, (SEQ ID NO:13)

(SEQ ID NO:14) AcK(Chel)F$_d$ CFW$_d$ KTCT-OH, AcK(Chel)DF$_d$ CFW$_d$ KTCT-OH, (SEQ ID NO:15)

(SEQ ID NO:14) AcK(Chel)F$_d$ CFW$_d$ KTCT-ol, AcK(Chel)DF$_d$ CFW$_d$ KTCT-ol, (SEQ ID NO:15)

(SEQ ID NO:16) (Chel)DF$_d$ CFW$_d$ KTCT-OH, K(Chel)DF$_d$ CFW$_d$ KTCT-ol, (SEQ ID NO:15)

(SEQ ID NO:17) K(Chel)KKF$_d$ CFW$_d$ KTCT-ol, K(Chel)KDF$_d$ CFW$_d$ KTCT-OH, (SEQ ID NO:18)

(SEQ ID NO:19) K(Chel)DSF$_d$ CFW$_d$ KTCT-OH, K(Chel)DF$_d$ CFW$_d$ KTCT-OH, (SEQ ID NO:15)

(SEQ ID NO:20) K(Chel)DF$_d$ CFW$_d$ KTCD-NH_2, K(Chel)DF$_d$ CFW$_d$ KTCT-NH_2, (SEQ ID NO:15)

(SEQ ID NO:18) K(Chel)KDF$_d$ CFW$_d$ KTCT-$NHNH_2$, AcK(Chel)F$_d$ CFW$_d$ KTCT-$NHNH_2$, (SEQ ID NO:14)

(SEQ ID NO:14) K(Chel)F$_d$ CFW$_d$ KTCT-ol, and F$_d$ CFW$_d$ KTCTK(Chel)-NH_2, (SEQ ID NO:21) wherein (Chel) is a radiometal-binding moiety.

42. A method according to claim 24, wherein said peptide contains at least one disulfide bond.

43. A method according to claim 42, wherein said peptide is a polypeptide.